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PATENT SPECIFICATION

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(54) OPHTHALMIC COMPOSITIONS

(71) We, MERCK & CO INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

Drugs such as pilocarpine and its various salts are currently used for the treatment of glaucoma. Although these drugs are useful they generally exhibit side effects such as extreme miosis, spasm of accomodation, night blindness and transient blurred vision. It has now been found that 1 - *t* - butylamino - 3 - (4 - morpholino 1,2,5 - thiadiazol 3 - yloxy) - 2 - propanol hydrogen maleate is effective in reducing intraocular pressure in both normal and hypertensive eyes, both of humans and of other animals, without the side effect associated with pilocarpine-type drugs.

1 - *t* - Butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate is a known compound useful as a β - adrenergic blocking agent, as is described in U.S. Patents 3,657,237, 3,729,469 and 3,655,663.

The present invention provides a method for treating glaucoma and of lowering intraocular pressure in a non-human animal that comprises topically applying to the eye of the said animal an effective amount of 1 - *t* - butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate. The present invention also provides an ophthalmic composition comprising, as active ingredient, 1 - *t* - butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazole - 3 - yloxy) - 2 - propanol hydrogen maleate, together with an ophthalmic carrier in the form of a solid, a vegetable oil, or a buffered isotonic liquid.

The ophthalmic compositions of the present invention are preferably solutions, ointments or solid inserts. Formulations of this compound may contain from 0.01 to 5% and especially 0.5 to 2% by weight of the active ingredient. Higher dosages, for example about 10%, or lower dosages can be used provided the dose is effective in lowering intraocular pressure. As a unit dosage form from 0.001 to 5.0 mg., preferably 0.005 to 2.0 mg., and especially 0.005 to 1.0 mg. of the compound is generally applied to the human eye.

The carrier may conveniently be organic or inorganic. Typical pharmaceutically acceptable carriers include water containing a buffering agent, isotonic mixtures of water and water-miscible solvents such as C_{1-6} alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum-based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone and isopropyl myristate. Among suitable buffering agents are sodium chloride, sodium borate, sodium acetate, and the gluconate buffers.

The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting and bodying agents, for example, polyethylene glycols 200, 300, 400, 600, 1,000, 1,500, 4,000, 6,000 and 10,000, bacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and that are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol and ethylenediamine tetracetic acid.

Additionally, suitable known ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles and isotonic sodium borate vehicles.

The pharmaceutical preparation may also be in the form of a solid insert. For example, a solid water-soluble polymer may be used as the carrier for the medicament. The polymer used to form the insert may be any water-soluble non-toxic polymer, for example, cellulose derivatives such as methylcel-

lulose; sodium carboxymethyl cellulose; (C_{1-5} hydroxyalkyl)cellulose such as hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose; acrylic acid derivatives such as polyacrylic acid salts, ethyl acrylates and polyacrylamides; natural products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar and acacia; the starch derivatives such as starch acetate, hydroxyethyl starch ethers, hydroxypropyl starch, and other synthetic derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl methyl ether, polyethylene oxide, neutralized carboxypolymethylene and xanthan gum, and mixtures of such polymers.

Preferably the solid insert is prepared from cellulose derivatives such as methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose or hydroxypropylmethyl cellulose or from other synthetic materials such as polyvinyl alcohol, polyvinyl pyrrolidone, polyethylene oxide or polyvinyl methylether. Hydroxypropyl cellulose, one of the preferred polymers for the preparation of the insert, is available in several polymeric forms, all of which are suitable in the preparation of these inserts. Thus, the product sold by Hercules, Inc. of Wilmington, Delaware, under the trade mark Klucel such as Klucel HF, HWF, MF, GF, JF, LF and EF, which are intended for food or pharmaceutical use, are particularly useful. The molecular weight of these polymers useful for the purposes described herein may be at least 30,000 and may even exceed 1,000,000. Similarly, an ethylene oxide polymer preferably having a molecular weight of 100,000 to 5,000,000 can be used. Further, for example, the polymer supplied by Union Carbide Co. under the trade mark Polyox may be used: this has a molecular weight of 50,000 to 5,000,000 and preferably 3,000,000 to 4,000,000. Other specific polymers which are useful are polyvinyl pyrrolidone having a molecular weight of from 10,000 to 1,000,000, preferably up to 350,000 and especially 20,000 to 60,000; polyvinyl alcohol having a molecular weight of from 30,000 to 1,000,000, particularly 30,000 to 400,000 and especially from 100,000 to 200,000; hydroxypropylmethyl cellulose having a molecular weight of from 10,000 to 1,000,000, particularly up to 200,000 and especially 80,000 to 125,000; methyl cellulose having a molecular weight of from 10,000 to 1,000,000, preferably 10,000 to 200,000 and especially 50,000 to 100,000; and Carbopol (Trade Mark for carboxyvinyl polymer) of B. F. Goodrich and Co. designated as grades 934, 940 and 941. It is clear that for the purpose of this invention the type and molecular weight of the polymer is not critical. Any water-soluble polymers can be used having an average molecular weight that will afford dissolution of the polymer and accordingly the medicament in any desired length of time. The inserts, therefore, can be prepared to allow for retention and accordingly effectiveness in the eye for any desired period. The insert can be, for example in the form of a square, rectangle, oval, circle, doughnut, semi-circle or quarter-moon shape. Preferably the insert is in the form of a rod, doughnut, oval or quarter moon. The insert can be readily prepared, for example, by dissolving the medicament and the polymer in a suitable solvent and the solution evaporated to afford a thin film of the polymer which can then be subdivided to prepare inserts of appropriate size. Alternatively the insert can be prepared by warming the polymer and the medicament and the resulting mixture molded to form a thin film. Preferably, the inserts are prepared by well known molding or extrusion procedures. The molded or extruded product can then be subdivided to afford inserts of suitable size for administration in the eye. The insert can be of any suitable size to readily fit into the eye. For example, castings or compression-molded films having a thickness of 0.25 mm. to 15.0 mm. can be subdivided to obtain suitable inserts. Rectangular segments of the cast or compressed film having a thickness between 0.5 and 1.5 mm. can be cut to afford shapes such as rectangular plates of 4×5—20 mm. or ovals of comparable size. Similarly, extruded rods having a diameter between 0.5 and 1.5 mm. can be cut into suitable sections to provide the desired amount of polymer. For example, rods of 1.0 to 1.5 mm. in diameter and about 20 mm. long are found to be satisfactory. The inserts may also be directly formed by injection molding. It is preferred that the ophthalmic inserts containing the medicament of the present invention be formed so that they are smooth and do not have any sharp edges or corners which could cause damage to the eye. Since the term smooth and sharp edges or corners are subjective terms, in this application these terms are used to indicate that excessive irritation of the eye will not result from the use of the insert.

The ocular medicinal inserts can also contain plasticizers, buffering agents and preservatives. Plasticizers suitable for this purpose must, of course, also be completely soluble in the lachrymal fluids of the eye. Examples of suitable plastizers that might be mentioned are water, polyethylene glycol, propylene glycol, glycerine, trimethylol propane, dipropylene glycol, tripropylene glycol and hydroxypropyl sucrose. Typically, such plasticizers can be present in the ophthalmic insert in an amount ranging from 1 to 40% by weight. A particularly preferred plasticizer is water which is present in amounts of at least 5% up to 40%. In actual practice, a water content of from 10% to 20% is preferred since it may be easily accomplished

and adds the desired softness and pliability to the insert.

When plasticizing the solid medicinal product with water, the product is contacted with air having a ratative humidity of at least 40% until said product picks up at least 5% water and becomes softer and more pliable. In a preferred embodiment, the relative humidity of the air is from 60% to 99% and the contacting is continued until the water is present in the product in amounts of from 10% to 20%.

Suitable water-soluble perservatives that may be included in the insert are sodium bisulfate, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, phenylmercuric borate, parabens, benzyl alcohol and phenylethanol. These agents may be present in amounts of from 0.001 to 5% by weight of solid insert, and preferably 0.1 to 2%.

Suitable water-soluble buffering agents are alkali metal and alkaline-earth metal carbonates, phosphates, bicarbonates, citrates and borates, such as sodium phosphate, citrate, borate, acetate, bicarbonate and carbonate. These agents may be present in amounts sufficient to obtain a pH of the system of between 5.5 to 8.0 and especially 7—8; usually up to 2% by weight of polymer. The insert may contain from 1 mg. to 100 mg. of water-soluble polymer, more particularly from 5 to 50 mg. and especially from 5 to 20 mg. The medicament makes up from 0.1 to 25% by weight of the insert.

The hydrogen maleate compound has been studied with respect to its ability to lower intraocular pressure of rabbits with experimental glaucoma induced by intraocular injection of α - chymotrypsin. This study demonstrated that the compound is very effective in lowering intraocular pressure after topical application. Pressure was reduced in the normal and the glaucomatous eye.

The following examples are given by way of illustration.

EXAMPLE 1

Solution Composition		
1 - *t* - Butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate (I)	1 mg.	15 mg.
Sodium phosphate monobasic .$2H_2O$	9.38 mg.	6.10 mg.
Dibasic sodium phosphate .$12H_2O$	28.48 mg.	16.80 mg.
Benzalkonium chloride	0.10 mg.	0.10 mg.
Sodium hydroxide q.s.	pH 6.8	pH 6.8
Water for injection q.s. ad.	1.0 ml.	1.0 ml.

(I), phosphate buffer salts, and benzalkonium chloride are added to and dissolved in water. The pH of the solution is adjusted to 6.8 with sodium hydroxide and the final solution diluted to volume. The solution is rendered sterile by filtration through a sterilizing filter.

EXAMPLE 2

1 - *t* - Butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate (I)	5 mg.
Petrolatum q.s. ad.	1 gram

Compound (I) and the petrolatum are aseptically combined.

EXAMPLE 3

1 - *t* - Butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate (I)	1 mg.
Hydroxypropylcellulose q.s.	12 mg.

Ophthalmic inserts are manufactured from compression molded films which are prepared on a Carver Press ('Carver' is a trade mark) by subjecting the powder mixture of the above ingredients to a compressional force of 12,000 lbs. (gauge) at 300°F for one to four minutes. The film is cooled under pressure by having cold water circulate in the platen. Ophthalmic inserts are then individually cut from the film with a rod-shaped punch. Each insert is placed into a vial, which is then placed in a humidity cabinet (88% R.H. at 30°C) for two to four days. After removal from the humidity cabinet, the vials are stoppered and then capped. The vials containing the hydrated insert are then autoclaved at 250°F for 1/2 hour.

EXAMPLE 4

1 - *t* - Butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate (I)	1 mg.
Hydroxypropyl cellulose q.s. ad.	12 mg.

Ophthalmic inserts are manufactured from a solvent cast film prepared by making a viscous solution of the powder using methanol as the solvent. The solution is placed on a polytetrafluoroethylene plate and allowed to dry at ambient conditions. After drying, the film is placed in an 88% R.H. cabinet until

it is pliable. Appropriately sized inserts are cut from the film.

EXAMPLE 5

1 - *t* - Butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate (I)	1 mg.
Hydroxypropyl methyl cellulose q.s. ad.	12 mg.

Ophthalmic inserts are manufactured from a solvent cast film which is prepared by making a viscous solution of the powder blend using a methanol/water solvent system (10 ml. methanol is added to 2.5 g. of powder blend, to which 11 ml. of water (in three divided portions) is added. The solution is placed on a polytetrafluoroethylene plate and allowed to dry under ambient conditions. After drying, the film is placed in an 88% R.H. cabinet until it is pliable. Appropriately sized inserts are then cut from the film.

EXAMPLE 6

1 - *t* - Butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate (I)	1 mg.
Hydroxypropylmethyl cellulose q.s. ad.	12 mg.

Ophthalmic inserts are manufactured from compression molded films which are prepared on a Carver Press by subjecting the powder mixture of the above ingredients to a compressional force of 12,000 lbs. (gauge) at 350°F for one minute. The film is cooled under pressure by having cold water circulate in the platen. Ophthalmic inserts are then individually cut from the film with a punch. Each insert is placed into a vial, which is then placed in a humidity cabinet (88% R.H. at 30°C) for two to four days. After removal from the humidity cabinet, the vials are stoppered and then capped. The vials containing the hydrated insert are then autoclaved at 250°F for one-half hour.

WHAT WE CLAIM IS:—

1. A method for treating glaucoma and of lowering intraocular pressure in a non-human animal that comprises topically applying to the eye of the said animal an effective amount of 1 - *t* - butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate.

2. An ophthalmic composition comprising, as active ingredient, 1 - *t* - butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazole - 3 - yloxy) - 2 - propanol hydrogen maleate, together with an ophthalmic carrier in the form of a solid, a vegetable oil, or a buffered isotonic liquid.

3. A composition as claimed in Claim 2, in which the carrier is a solid water-soluble polymer.

4. A composition as claimed in Claim 3, in which the carrier is hydroxypropyl cellulose.

5. An ophthalmologically acceptable water-soluble polymeric insert comprising an effective amount of 1 - *t* butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate.

6. A method of preparing an ophthalmic composition that comprises admixing 1 - *t* - butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazole - 3 - yloxy) - 2 - propanol hydrogen maleate with an ophthalmic carrier in the form of a solid, a vegetable oil, or a buffered isotonic liquid.

7. A method of preparing an insert as claimed in Claim 5 that comprises admixing a solid water-soluble polymer with 1 - *t* - butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazole - 3 - yloxy) - 2 - propanol hydrogen maleate.

8. A composition as claimed in Claim 2 substantially as hereinbefore described in Example 1 or 2.

9. An insert as claimed in Claim 5 substantially as hereinbefore described in any one of Examples 3 to 6.

10. A method as claimed in Claim 6 substantially as hereinbefore described in Example 1 or 2.

11. A method as claimed in Claim 7 substantially as hereinbefore described in any one of Examples 3 to 6.

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it is pliable. Appropriately sized inserts are cut from the film.

EXAMPLE 5

1 - *t* - Butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate (I)	1 mg.
Hydroxypropyl methyl cellulose q.s. ad.	12 mg.

Ophthalmic inserts are manufactured from a solvent cast film which is prepared by making a viscous solution of the powder blend using a methanol/water solvent system (10 ml. methanol is added to 2.5 g. of powder blend, to which 11 ml. of water (in three divided portions) is added. The solution is placed on a polytetrafluoroethylene plate and allowed to dry under ambient conditions. After drying, the film is placed in an 88% R.H. cabinet until it is pliable. Appropriately sized inserts are then cut from the film.

EXAMPLE 6

1 - *t* - Butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate (I)	1 mg.
Hydroxypropylmethyl cellulose q.s. ad.	12 mg.

Ophthalmic inserts are manufactured from compression molded films which are prepared on a Carver Press by subjecting the powder mixture of the above ingredients to a compressional force of 12,000 lbs. (gauge) at 350°F for one minute. The film is cooled under pressure by having cold water circulate in the platen. Ophthalmic inserts are then individually cut from the film with a punch. Each insert is placed into a vial, which is then placed in a humidity cabinet (88% R.H. at 30°C) for two to four days. After removal from the humidity cabinet, the vials are stoppered and then capped. The vials containing the hydrated insert are then autoclaved at 250°F for one-half hour.

WHAT WE CLAIM IS:—

1. A method for treating glaucoma and of lowering intraocular pressure in a non-human animal that comprises topically applying to the eye of the said animal an effective amount of 1 - *t* - butylamino - 3 - (4 morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate.

2. An ophthalmic composition comprising, as active ingredient, 1 - *t* - butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazole - 3 - yloxy) - 2 - propanol hydrogen maleate, together with an ophthalmic carrier in the form of a solid, a vegetable oil, or a buffered isotonic liquid.

3. A composition as claimed in Claim 2, in which the carrier is a solid water-soluble polymer.

4. A composition as claimed in Claim 3, in which the carrier is hydroxypropyl cellulose.

5. An ophthalmologically acceptable water-soluble polymeric insert comprising an effective amount of 1 - *t* butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol hydrogen maleate.

6. A method of preparing an ophthalmic composition that comprises admixing 1 - *t* - butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazole - 3 - yloxy) - 2 - propanol hydrogen maleate with an ophthalmic carrier in the form of a solid, a vegetable oil, or a buffered isotonic liquid.

7. A method of preparing an insert as claimed in Claim 5 that comprises admixing a solid water-soluble polymer with 1 - *t* - butylamino - 3 - (4 - morpholino - 1,2,5 - thiadiazole - 3 - yloxy) - 2 - propanol hydrogen maleate.

8. A composition as claimed in Claim 2 substantially as hereinbefore described in Example 1 or 2.

9. An insert as claimed in Claim 5 substantially as hereinbefore described in any one of Examples 3 to 6.

10. A method as claimed in Claim 6 substantially as hereinbefore described in Example 1 or 2.

11. A method as claimed in Claim 7 substantially as hereinbefore described in any one of Examples 3 to 6.

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